

Pathophysiology of anaphylaxis

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Purpose of review

This review aims to provide an overview of the evolving understanding of the pathophysiology of anaphylaxis.

Recent findings

Immunopathologic mechanisms of anaphylaxis have traditionally focused on the IgE-dependent and IgE-independent release of mediators from mast cells and basophils. There are accumulating data supporting the significance of alternative pathways of anaphylaxis. Increasing attention has also focused on the internal compensatory mechanisms activated in response to anaphylaxis.

Summary

Recent advances will enhance understanding of the pathophysiology of anaphylaxis and might have future implications for diagnosis and management.

Keywords

anaphylaxis, bradycardia, mechanisms, pathophysiology

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Introduction

Anaphylaxis is an acute potentially life-threatening multisystem syndrome caused by the sudden release of mast cell and basophil-derived mediators into the systemic circulation [1]. It most often results from immunologic reactions to foods, medications, and insect stings, but any agent capable of producing a sudden, systemic degranulation of mast cells or basophils can produce it [2]. It may be ‘allergic’ or ‘immunologic’ [IgE-dependent or IgE-independent (i.e. IgG mediated or immune complex/complement mediated)] or nonimmunologic [3]. Its diagnosis rests primarily on probability and clinical pattern recognition.

Anaphylaxis consists of some or all of the following signs and symptoms: pruritus, diffuse erythema, urticaria, and/or angioedema; laryngeal edema; bronchospasm; hypotension; syncope; and/or cardiac arrhythmias. Other symptoms can occur such as a generalized flushing sensation, headache, lightheadedness, nausea, vomiting, uterine cramps, and feeling of impending doom. Anaphylaxis often causes signs and symptoms within 5–30 min, but some reactions may not develop for several hours. Respiratory compromise and cardiovascular collapse are responsible for most fatalities [2,4]. The more rapid the onset of the signs and symptoms of anaphylaxis following exposure to an offending stimulus, the more likely the reaction will be life threatening. Retrospective analysis of 214 anaphylaxis fatalities determined that the interval between eating a culprit food and fatal cardiopulmonary arrest averaged 25–35 min,

which was longer than for drugs (mean, 5 min in-hospital; 10–20 min prehospital) or insect stings (10–15 min) [4].

A PubMed (US National Library of Medicine) search for ‘anaphylaxis pathophysiology’ yields more than 300 reviews published in the English language, but most focus on particular clinical presentations (e.g. food anaphylaxis) or cell types (e.g. mast cells). We located only four overview articles [2,5–7]. We aim to focus on some of the more novel and emerging areas of investigation into the pathophysiology of anaphylaxis.

Immunologic anaphylaxis

The pathogenesis of anaphylaxis arguably is fairly obscure, but murine models demonstrate two distinct mechanisms that probably also apply to humans. The first, the IgE-dependent reaction, is both interleukin (IL)-4 and IL-4 receptor dependent and is caused by the allergen-induced cross linking of high-affinity FcεRI receptors present on mast cells and basophils, from which subsequent release of inflammatory mediators and cytokines causes the increased vascular permeability and smooth muscle contraction associated with clinical anaphylaxis [8,9^{*}]. The second mechanism is IgE-independent, involves the binding of IgG, and requires proportionately more antigen and antibody than the IgE-dependent pathway. Depending on the experimental system, IgG-dependent anaphylaxis may involve either macrophages or basophils [8,10,11,12^{*}]. Both mechanisms release platelet activating factor (PAF), but only the IgE-dependent mechanism releases histamine (Fig. 1) [8,10,13].

Multiple additional protein motifs, receptors, channels, and molecular signals act at various levels to modulate anaphylaxis induction, however. These have been characterized best in murine models and include the complex interactions of cell-associated tyrosine kinases, intracellular immunoreceptor tyrosine-based activation motifs (ITAMs), intracellular immunoreceptor tyrosine-based inhibition motifs (ITIMs), Src homology 2-containing tyrosine phosphatases 1 and 2 (SHP1 and SHP2), and Src homology 2-containing inositol phosphatase (SHIP) [8] provides an overview.) Sphingosine kinases and Tec kinases also are determinants of mast cell responsiveness [14,15[•],16].

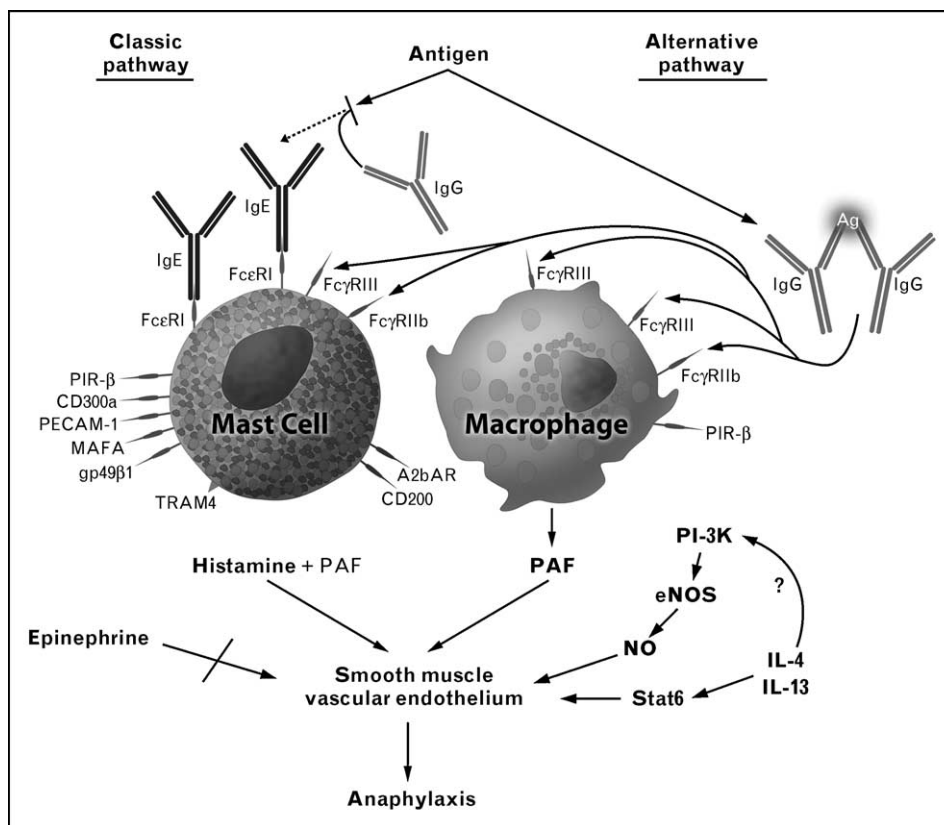
IgG-dependent anaphylaxis has not been proven in humans. However, human IgG receptors are capable of activating macrophages to release PAF [8], which can activate mast cells *in vitro* [17[•]]. Therefore, PAF may contribute to human anaphylaxis [18,19[•]].

Key points

- Anaphylaxis can be precipitated by both immunological and nonimmunological mechanisms.
- Anaphylaxis may be associated with myocardial depression, arrhythmias, and myocardial ischemia.
- The pathophysiology of anaphylaxis involves multiple interactions and pathways, including some internal compensatory mechanisms.
- Although uncommon, bradycardia can occur in anaphylaxis and might comprise part of a poorly understood compensatory mechanism for hypovolemic shock.

Rare individuals have experienced anaphylaxis after receiving therapeutic preparations of IgG anti-IgE antibodies (omalizumab) [20,21]. Omalizumab blocks binding of IgE to FcεRI receptors and does not bind FcεRI-associated IgE [8,22]. These anaphylactic events conceivably could be mediated by IgG, with drug-IgG

Figure 1 Classic and alternative pathways in murine anaphylaxis



Antigen causes anaphylaxis in the mouse by (a) cross-linking IgE bound to mast cell FcεRI receptors, which stimulates release of histamine and smaller amounts of PAF (IgE dependent, or 'classic pathway'), or (b) binding in large quantities with IgG to form IgG-antigen immune complexes that cross-link macrophage FcγRIII receptors, which stimulates release of PAF but not histamine (IgG dependent, or 'alternative pathway'). Basophil interactions are not depicted. Histamine and PAF both induce smooth muscle constriction and enhance vascular permeability associated with anaphylaxis. IgG provides negative feedback to the classic pathway. IL-4, IL-13, and nitric oxide exacerbate anaphylaxis by enhancing cellular responsiveness to proinflammatory mediators. Epinephrine relaxes smooth muscle and decreases vascular permeability. Adapted with permission from [4]. eNOS, endothelial nitric oxide synthase; IL, interleukin; NO, nitric oxide.

binding to patient IgE [8]. IgE-independent anaphylaxis has also been reported in some individuals receiving another monoclonal antibody preparation, infliximab [23,24]. More human data are needed to clarify the causative mechanism.

All mast cells express *c-kit*, a surface membrane receptor with tyrosine kinase activity. A D816V *c-kit* mutation leads to clonal mast cell activation associated with severe anaphylaxis [25^{••}]. The number of mast cells is normal, but the affected patients have shown an atypical expression of CD25.

Nonimmunologic anaphylaxis

Some agents can cause degranulation of mast cells and basophils without help from immunoglobulins thus leading to nonimmunologic anaphylaxis. Examples include physical factors, such as heat or cold, and opioids and vancomycin, which directly degranulate mast cells [26].

Chemical mediators of anaphylaxis

During anaphylaxis, mast cell and basophil degranulation releases multiple biochemical mediators and chemotactic substances, including cytokines; preformed granule-associated substances such as histamine, tryptase, chymase, heparin, and carboxypeptidase A3; and newly generated lipid-derived mediators such as PAF, prostaglandin D₂, leukotriene B₄, and the cysteinyl leukotrienes, LTC₄, LTD₄, and LTE₄ [2,26,27]. Anaphylaxis also depends on cellular responsiveness to these mediators. IL-4 and IL-13 are cytokines important in the initial responses to anaphylaxis. No comparable human studies have been conducted, but anaphylactic effects in the mouse depend on IL-4R α -dependent IL-4/IL-13 activation of the transcription factor, signal transducer, and activator of transcription 6 (STAT-6). The most rapid, dramatic effect of IL-4 in murine anaphylaxis is a three-fold to six-fold increase in cellular responsiveness to inflammatory and vasoactive mediators, including histamine, leukotrienes, serotonin, and PAF [8]. In mice, increased IL-4 receptor signaling also enhances anaphylaxis risk [28[•]].

IL-25 produced by Th17 lymphocytes induces eosinophilia and also upregulates tissue expression of IL-4, IL-5, and IL-13 [29]. Conversely, regulatory T lymphocytes can suppress mast cell release of histamine, thus inhibiting anaphylaxis [30,31]. (Details on antigen presentation and allergen-specific T-cell responses are reviewed elsewhere [32[•]].)

The human roles of PAF and PAF acetylhydrolase, the enzyme that inactivates PAF, are becoming increasingly clear for anaphylaxis. In a prospective controlled

study [18], serum PAF levels correlated directly and PAF acetylhydrolase levels correlated indirectly with the severity of anaphylaxis. In companion retrospective analysis, PAF acetylhydrolase activity was significantly lower in individuals experiencing fatal peanut-induced anaphylaxis than for five control groups.

A mouse model of anaphylaxis indicates that IL-33 can induce antigen-independent systemic anaphylaxis and can directly induce degranulation, and eicosanoid and cytokine production in IgE-sensitized mast cells [33[•]]. The role of IL-33 in human anaphylaxis has not been elucidated.

Eosinophils may be proinflammatory (e.g. through release of cytotoxic granule-associated proteins) or anti-inflammatory (e.g. through metabolism of vasoactive mediators) [26,34]. A guinea pig model of anaphylaxis suggests that eosinophils already present in chronically inflamed airways may participate in the acute response to allergen exposure, as well as the anticipated late-phase response [35]. Potential implications for humans have not been studied.

Histamine and tryptase

Histamine exerts its effects through its four receptors. The stimulation of H1 and H2 receptors precipitates flushing, hypotension, and tachycardia, and H1 receptors alone lead to manifestations of tachycardia, pruritus, rhinorrhea, and bronchospasm [36]. Serum histamine levels also correlate with the severity of cardiopulmonary manifestations of anaphylaxis [37,38]. Canine models of anaphylaxis suggest H3 receptors influence cardiovascular responses to norepinephrine [39], whereas murine models suggest H4 receptors might be involved in chemotaxis and mast cell cytokine release and might also help to mediate pruritus [40,41]. However, potential human implications have not been studied.

Tryptase is a protease concentrated in the secretory granules of human mast cells, although basophils contain trace amounts [42]. β -tryptase (mature tryptase) is enzymatically active and is released when these cells degranulate. Tryptase can activate complement, coagulation pathways, and the kallikrein-kinin contact system with the potential clinical consequences of angioedema, hypotension, and disseminated intravascular coagulation [4,26]. Tryptase levels generally correlate with the clinical severity of anaphylaxis. However, the route of allergen exposure appears to influence tryptase levels, possibly related to the subtype of mast cell the culprit allergen first encounters. Mast cells that predominate in the pulmonary and intestinal mucosa contain much less tryptase per cell than those in connective tissues [43]. Thus, tryptase levels may correlate poorly in food anaphylaxis, for example.

Recent reports concerning insect sting anaphylaxis suggest closer scrutiny to basal tryptase levels might be appropriate, especially in individuals who experienced hypotensive episodes, to exclude mastocytosis or a monoclonal mast cell disorder [25^{••},44[•],45[•]].

Nitric oxide in anaphylaxis

Nitric oxide, a potent autacoid vasodilator, participates in the homeostatic control of vascular tone and regional blood pressure [46,47]. However, its net effects in anaphylaxis appear to be detrimental vascular smooth muscle relaxation and enhanced vascular permeability [48].

The binding of histamine to H1-receptors initiates phospholipase-C-dependent calcium mobilization, converting L-arginine to nitric oxide through the activity of various isoforms of nitric oxide synthase (NOS). The constitutively expressed isoforms, endothelial NOS (eNOS) and neuronal NOS (nNOS), presumably produce low amounts of nitric oxide for physiologic and/or anti-inflammatory functions. Conversely, inflammation-associated expression of inducible nitric oxide synthase (iNOS) and subsequent overproduction of nitric oxide and activation of guanylate cyclase have been implicated in detrimental cardiovascular effects associated with septic shock. Many have presumed that this mechanism also applies in anaphylaxis [49]. However, subsequent studies in knockout mice suggest that eNOS, rather than iNOS, is a critical mediator of PAF-mediated anaphylactic shock [50]. Similar human data are unavailable, but these findings suggest NOS involvement in anaphylaxis may be more complex than previously thought.

Serum factors and other inflammatory pathways

During severe episodes of anaphylaxis, there is activation of complement, coagulation pathways and the kallikrein-kinin contact system. Many of the supporting data were obtained during experimental insect sting anaphylaxis. Decreases in C4 and C3 and generation of C3a have been observed. Evidence for coagulation pathway activation during severe anaphylaxis includes decreases in factor V, factor VIII, and fibrinogen, and fatal disseminated intravascular coagulation in some instances [4,38]. Decreased high molecular weight kininogen and the formation of kallikrein-C1 inhibitor and factor XIIa-C1 inhibitor complexes indicate kallikrein-kinin contact system activation [38,51].

Modulatory mediators

Some mediators may have anti-inflammatory and modulatory effects that limit anaphylaxis. For example, heparin modulates tryptase activity, opposes complement, and

inhibits clotting, plasmin, and kallikrein [38]. Chymase stimulates the conversion of angiotensin I into angiotensin II, independent of angiotensin converting enzyme, and might potentially help to decrease the severity of hypotension [52].

Shock organs in anaphylaxis

The organs predominantly affected by anaphylaxis vary from species to species and direct the clinical course of anaphylaxis. Determinative factors include variations in immune response; location of smooth muscle; and distribution, rate of degradation and responsiveness to proinflammatory mediators. In humans, the predominant shock organs are the lungs and the heart [4,53]. An emerging view is that anaphylaxis has features of both distributive shock and hypovolemic shock, with fluid extravasation causing reduced venous return, as well as myocardial depression [6]. Data also suggest splenic involvement may be more significant than previously thought [54]. Our review will focus on the heart. (Shock organs for other animal species are reviewed elsewhere [55].)

Cardiovascular manifestations of anaphylaxis

Chemical mediators of anaphylaxis appear to affect the myocardium directly and an increased cardiac mast cell density suggests anaphylaxis might be particularly severe in individuals with certain underlying cardiovascular diseases [56[•],57]. However, the heart can be the primary target of anaphylaxis, even in individuals with no prior cardiovascular disease. One report described two previously healthy individuals who developed profound myocardial depression during anaphylaxis [58]. Echocardiography, nuclear imaging, and hemodynamic measurements confirmed the presence of myocardial dysfunction. Intra-aortic balloon counterpulsation was necessary for hemodynamic support up to 72 h because of persistent myocardial depression, even though other clinical signs of anaphylaxis had resolved. Both individuals recovered with no evidence of residual dysfunction.

Effects on myocardium, conductive system, and coronary vasculature

Anaphylaxis has been associated with myocardial ischemia and conduction defects, including arrhythmias and T-wave abnormalities [56[•],59]. It is unclear if these changes are a result of direct action of the mediators on the myocardium, exacerbation of preexisting myocardial insufficiency, endogenous release of epinephrine by the adrenal medulla in response to stress, or to therapeutically administered epinephrine [38,56[•],58,59]. Histamine and PAF can also directly act on the conduction system and coronary vasculature to elicit these cardiac manifestations

[56,57,60]. Calcitonin gene-related peptide might also help to relax vascular smooth muscle and counteract coronary artery vasoconstriction [61–63].

Responses to fluid shifts

Massive fluid shifts can occur during anaphylaxis due to increased vascular permeability, as up to 35% of the intravascular volume can leak into the periphery within 10 min [64]. Compensatory responses include release of endogenous catecholamines, angiotensin II, and endothelins. When adequate, these responses may be life saving, independent of any medical intervention.

Some individuals experience abnormal elevations of peripheral vascular resistance (maximal vasoconstriction yet shock persists due to diminished intravascular volume) [65], whereas others have decreased systemic vascular resistance, despite elevated levels of catecholamines [66]. These differences have important clinical implications because the latter scenario may respond favorably to therapeutic doses of vasoconstrictor agents, whereas the former is vasoconstrictor unresponsive and requires large-volume fluid resuscitation.

Body posture

The individual's posture during anaphylaxis might also impact survival. In a retrospective review, four of ten prehospital anaphylaxis fatalities were associated with assumption of an upright or sitting position [67]. Postmortem findings were consistent with pulseless electrical activity and inadequate venous return attributed to fluid shifts.

Bradycardia in anaphylaxis

Tachycardia is the rule, but bradycardia may occur and thus may not be as useful to distinguish anaphylaxis from a vasodepressor reaction as previously presumed. Relative bradycardia (initial tachycardia followed by a reduction in heart rate despite worsening hypotension) has been reported previously in experimental settings of insect sting anaphylaxis, as well as in trauma patients [38,51,68–70].

Two distinct phases of physiologic response occur in mammals subjected to hypovolemia. The initial phase is a baroreceptor-mediated, sympatho-excitatory response composed of increased cardiac sympathetic drive and the simultaneous withdrawal of resting vagal drive, which together produce tachycardia and peripheral vasoconstriction [69]. As effective blood volume decreases 20–30%, the second phase follows, characterized by withdrawal of vasoconstrictor drive; relative or absolute bradycardia; increased vasopressin; further catecholamine release as

the adrenal axis becomes more active; and hypotension [69,70]. Atropine administered therapeutically in this scenario reverses the bradycardia but not the hypotension.

Clinical implications of bradycardia in human anaphylactic shock have not been studied. However, a retrospective analysis of approximately 11 000 trauma individuals determined that mortality was lower in the 29% of hypotensive patients who were bradycardic than for those hypotensive patients with tachycardia, after adjusting for other mortality factors [70]. Thus, there may be a compensatory role for bradycardia in this hypotensive scenario.

Conduction defects and sympatholytic medications may also produce bradycardia [2]. Excessive venous pooling with decreased venous return (also seen in vasodepressor reactions) may activate tension-sensitive sensory receptors in the infero-posterior portions of the left ventricle, thus resulting in a cardio-inhibitory (Bezold–Jarisch) reflex that stimulates the vagus nerve and causes bradycardia [26].

Bradycardia has also been observed in porcine anaphylaxis induced experimentally by various liposomal preparations. Adenosine and C5a have been implicated [71].

Conclusion

Anaphylaxis involves numerous immunopathologic mechanisms and complex interactions. Well-characterized animal models of anaphylaxis clearly would help to facilitate understanding of these mechanisms, which might ultimately aid in its diagnosis and management.

Acknowledgement

The authors have no conflicts of interest to declare.

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